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14. ABSTRACT Our goal is to define the clinical phenotype of cognitive impairment and dementia in older veterans who have been exposed to TBI. Our hypothesis is that TBI in early to mid-life is associated with a dementia phenotype that has features distinguishable from AD. In the first year, we completed the screening survey portion of the study and found that over half of the veterans surveyed (n=298) had a history of head injury, with over 20% requiring hospitalization. Those with TBI were more likely to report mood, anxiety, substance use disorder, and PTSD symptoms over the course of their lifetime, have active PTSD symptoms, and have subjective memory complaints (all $p < 0.05$). A manuscript based on these results has been submitted to a peer-reviewed journal. Data collection for the cross-sectional study phase has recently been completed. Preliminary results, presented in an abstract, showed that executive function may be decreased in participants with TBI history compared to controls. We will soon begin analyzing the data from the full study: 73 participants with TBI history and 70 controls. The results will determine if a clinical phenotype of dementia in individuals with TBI exists, which has relevance for future treatment.

15. SUBJECT TERMS
Traumatic brain injury (TBI), dementia, chronic traumatic encephalopathy (CTE), post-traumatic stress disorder (PTSD), aging

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Introduction

One possible long-term consequence of traumatic brain injury (TBI) is dementia. TBI in early and mid-life is associated with an increased risk of late-life dementia, with relative risks in the order of 2.5 to 5.0 [1-3]. Military veterans are at high risk of TBI during combat as well as during peacetime service [4]. The goal of this project is to define the clinical phenotype of late-life dementia in veterans who have been exposed to TBI. Our hypothesis is that TBI in early to mid-life is associated with a dementia phenotype that has features distinguishable from Alzheimer's disease (AD). Specifically, we hypothesize that: 1) veterans with TBI-associated cognitive impairment or dementia will have higher levels of symptoms of depression, anxiety, and Parkinsonism compared to veterans with cognitive impairment/dementia who have not experienced a TBI, and 2) veterans with TBI-associated cognitive impairment or dementia will have prominent deficits in executive function, compared to veterans with cognitive impairment/dementia who have not had a TBI. This cross-sectional study will lead to a better understanding of the features of TBI-associated cognitive impairment and dementia in retired military veterans. The project will develop clinical criteria to allow accurate and early diagnosis and is critically important to the Department of Defense, the Veterans Administration, as well as to society at large.

Key Words

Traumatic brain injury (TBI), dementia, chronic traumatic encephalopathy (CTE), post-traumatic stress disorder (PTSD), aging

Overall Project Summary

Task 1: Screen retired military service men and women at each site [Armed Forces Retirement Home (AFRH), Washington, DC and Veterans Home of California-Yountville (VHC-Yountville)]

Subtask 1a. Planning and Regulatory Review

Completed in the first two quarters of Year 1 and reported in Year 1 Annual Report.

Subtask 1b. Screen retired service members at AFRH and VHC-Yountville

Data collection details, data analysis, and results reported in the Year 1 Annual Report. The manuscript describing the results has been submitted to a peer-reviewed journal.

Task 2. Enroll retired service members at AFRH and VHC-Yountville

Potentially eligible participants were identified using information from: (1) the survey in which participants consented to be contacted for a future study, and (2) chart review through an IRB-approved Waiver of Authorization for Recruitment. The potentially eligible participants were contacted and asked if they were interested in taking part in the cross-sectional study. After a thorough explanation of the study and procedures, those interested in participating were scheduled for a study visit and consented before any study procedures took place. The inclusion and exclusion criteria are listed in the appendix. If, upon learning further information, the patient does not meet eligibility criteria, they were considered a screen failure and do not go through study procedures.

Subtask 2a. Evaluate both cases and controls

Data for each participant (TBI or control) was collected over two separate appointments, each taking no longer than 90 minutes. The first visit involved signing the consent and HIPAA documents, gathering basic demographic and medical history data, various health and lifestyle questionnaires, and a neurological examination. All the neuropsychological tests took place at the second visit. As of 10/15/14, data collection is complete. We have collected data from 143 individuals, 73 with a history of TBI requiring medical care, and 70 controls.

Preliminary results on the first 118 participants (61 TBIs and 57 controls) were presented at the Alzheimer's Association International Conference, July 2014. For the 61 participants with history of TBI, the average age of first head injury was 27; 74% of TBI participants reported more than one TBI and 72% reported loss of consciousness after at least one injury. Military-related TBI was found in 26% of TBI participants.

Comparing group demographics, age and gender differed, with the TBI group being younger and more likely to be male ($p < 0.05$). Race, education, and years of military service did not differ. History of diabetes was more prevalent in people with TBI ($p < 0.05$), as was history of drug or alcohol abuse ($p < 0.001$). The TBI group also had more current symptoms of depression and PTSD (both $p < 0.05$), although both were below levels of clinical significance.

Table 1 below shows that the two groups did not differ on tests of general cognition, learning and memory, or language (adjusting for age, gender, race, and education). Table 2 below shows that the two groups did differ on several tests of processing speed and executive function. Further analyses additionally adjusting for diabetes, substance abuse history, depression, and PTSD indicated that the relationship between TBI and processing speed/executive functioning was attenuated, but still present. These preliminary results indicate that older veterans with a

history of TBI may have a different cognitive profile. TBI is associated with increased history of substance abuse, depression, and PTSD, but that may not entirely account for lower performance.

Table 1: Differences between TBI and control participants for tests of general cognition, learning and memory, and language.

	Control	TBI	*p*-value
	Mean (SD)	Mean (SD)	
General Cognition			
MMSE	28.0 (1.5)	27.6 (2.6)	0.20
Learning and Memory			
AVLT Learning Trials	32.9 (8.2)	32.9 (8.2)	0.85
AVLT Delayed Recall	4.3 (3.0)	5.2 (2.8)	0.32
Language			
BNT Total Score	26.5 (2.9)	26.3 (3.3)	0.36
Animals	17.9 (4.9)	18.2 (5.0)	0.80

SD = Standard deviation, * = *p*-values adjusted for age, gender, race, education

Table 2: Differences between TBI and control participants for tests of processing speed and executive function.

	Control	TBI	*p*-value
	Mean (SD)	Mean (SD)	
Processing Speed/Executive Functioning			
Trails A (sec.)	49.1 (19.5)	54.6 (29.4)	0.04
Trails B (sec.)	132.5 (64.3)	147.5 (78.7)	0.04
Digit Symbol	37.4 (9.3)	34.8 (10.9)	0.03
Flanker Task	8.05 (0.78)	7.67 (0.86)	0.01
Set Shifting Task	6.72 (1.15)	6.89 (1.10)	0.74
N-Back Task	1.81 (0.88)	1.81 (0.88)	0.79
Able to do N-Back, n (%)	52 (91.2%)	47 (79.7%)	0.08
Antisaccade task	28.7 (8.5)	28.6 (8.4)	0.48

SD = Standard deviation, * = *p*-values adjusted for age, gender, race, education

Key Research Accomplishments

- Screening survey developed, administered to 298 veterans, and data analyzed.
- Survey data manuscript currently under review.
- Cross-sectional study completed with clinical and neuropsychological data from over 140 veterans.
- Cross-sectional data analysis started and manuscript in preparation.

Conclusion

In the first year of the project we developed and administered a survey to nearly 300 veterans residing in two veterans homes. We found that TBI is a common occurrence in the older veterans residing in veterans homes, affecting over half of the population, and is associated with a greater history of psychiatric disorders and current cognitive symptoms. The study results indicate that this understudied group of older veterans is likely a fruitful population for examining TBI-related cognitive impairment.

In this past year we completed data collection for the cross-sectional study, establishing a cohort of over 140 veterans, approximately half with a history of TBI. Preliminary results indicate that the participant with TBI history are more likely to have lower scores on tests of executive function and processing speed, even after adjusting for confounding variables. We are currently beginning the final analysis now that data collection is complete, and beginning manuscript preparation.

Understanding the features of cognitive impairment and dementia in retired military veterans, and developing clinical criteria to allow accurate and early diagnosis is critically important to the Department of Defense, the Veterans Administration, as well as to society at large. For service members at increased risk of AD-type neurodegeneration as a consequence of their service in combat, early recognition is essential in order to implement preventive therapies.

Publications, Abstracts, and Presentations

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2. Peltz C, Kramer J, Kenney K, Diaz-Arrastia R, Yaffe K. Cognitive effects of TBI in older veterans. Alzeimer's Association International Conference; 2014; Copenhagen, Denmark: Alzheimer's & Dementia 2014; 10(4):P205. DOI:10.1016/j.jalz.2014.04.258
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5. Wang S, Culver C, Peltz C, Diaz-Arrastia R, Kenney K, Kramer J, Awoke S, Yaffe K. Traumatic Brain Injury and Comorbid Neuropsychiatric Symptoms in an Older Veteran Population. Under Review.

Inventions, Patents, and Licenses

N/A

Reportable Outcomes

N/A

Other Achievements

- Utilizing pilot data, we applied to the DOD to expand on this project in order to obtain blood samples for biomarker analysis and increase our cohort to include participants with mild AD. Dr. Kristine Yaffe will serve as the PI of the project with Dr. Ramon Diaz-Arrastia as Co-PI. The project has been funded and we received the Notice of Award on 9/22/14. There is no scientific or funding overlap with this project.

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2. Guo Z, Cupples LA, Kurz A, et al. Head injury and the risk of AD in the MIRAGE study. Neurology 2000;54:1316-1323.
3. Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000;55:1158-1166.
4. Okie S. Traumatic brain injury in the war zone. N Engl J Med 2005;352:2043-2047.

Appendix

Inclusion Criteria

- TBI Participants:
  - Aged 50-95
  - Resident in the independent living facility at the VHC-Yountville or the AFRH-Washington D.C.
  - Can speak, read, and understand English
  - Capacity to provide consent to participate in research
  - MMSE score ≥ 20
  - History of traumatic brain injury: required to have sought medical treatment (ER visit, doctor visit, hospitalization) after a head injury
- Controls (without a history of TBI):
  - Aged 50-95
  - Resident in the independent living facility at the VHC-Yountville or the AFRH-Washington D.C.
  - Can speak, read, and understand English
  - Capacity to provide consent to participate in research
  - MMSE score ≥ 20
  - No history of TBI or concussion (defined as no head injury resulting in being dazed, having a memory gap, loss of consciousness, or medical treatment)

Exclusion Criteria

- TBI Participants:
  - History of penetrating brain injury
  - Currently active disabling neurological or psychiatric condition (such as epilepsy, multiple sclerosis, cortical stroke, hypoxic-ischemic encephalopathy, encephalitis or schizophrenia)
  - Lack of competence to provide consent to participate in research
  - No verbal and oral fluency English
  - Non-correctable vision or hearing impairments (severe enough to impair testing)
- Controls (without a history of TBI):
  - Currently active disabling neurological or psychiatric condition (such as epilepsy, multiple sclerosis, cortical stroke, hypoxic-ischemic encephalopathy, encephalitis or schizophrenia)
  - Lack of competence to provide consent to participate in research
  - No verbal and oral fluency English
  - Non-correctable vision or hearing impairments (severe enough to impair testing)